REMARKS

This is a full and timely response to the final Office Action mailed May 11, 2007. Reconsideration of the application and allowance of presently pending claims as amended, are respectfully requested.

A. Present Status of Patent Application

Independent claims 1, 38 and 54 have been directly amended, and the remaining claims indirectly amended as they depend from one of the amended Independent claims. Claims 43, 45-46, 57, 59, 61 and 69-83 have been cancelled without prejudice, waiver or estoppel. Claims 23-37 and 84-102 had been previously withdrawn pursuant to a Restriction Requirement. New claim 103 has been added. Claims 1-22, 38-42, 44, 47-56, 58, 60, 62-68, and 103 remain pending.

Support for the amendments to claims 1, 38, and 54 are found, for example at paragraphs 0042-0046 of the published application. Support for the amendments to claims 2-4 and 41 is found at least in Fig 2 and paragraph 0112. Support for the amendment to claim 5 is found at least in Fig 1 and paragraph 0042. Support for the amendments to claims 39 and 42 is found at least in paragraph 0078. Support for the amendment to claim 12, and for new claim 103, is found in paragraph 0034.

B. Response to Rejections

1. Provisional Double Patenting Rejection

The provisional rejection of claims 1-8, 12-15, 19, 20, 38-44, 46-49, 52, 69-75, 77-79, and 82 on the ground of nonstatutory obviousness-type double patenting over the claims of co-pending U.S. application 11/187,757 has been noted. Should the provisional rejection mature into a double-patenting rejection which is the sole ground of rejecting the present claims, consideration will be given to filing the appropriate terminal disclaimer.

2. Rejection under 35 U.S.C. §102(b) over *Weers et al.* WO99/16422 and Block (J. Pharm Sci, Vol 62, No. 4, Pages 617-621 (1973)

Claims 1-22 were rejected under 35 USC 102(b) as anticipated by *Weers et al.* "as evidenced by *Block*." While applicants contend that even the unamended claims distinguish over the cited references, applicants have nonetheless amended independent claim 1 to further clarify the distinctions, in particular with regard to the powder state of the composition and suitability for pulmonary administration. The remaining claims are indirectly amended as they depend from amended independent claim 1.

Initially, it should be noted that the claims refer to physical characteristics of two different (but related) elements: the active agent particles themselves, and the particulates comprising the active agent particles plus matrix.

As amended, claim 1 recites a pharmaceutical formulation for pulmonary administration, the formulation comprising particulates consisting essentially of an active agent particle each element of which is characterized by the specified physical parameters.

Weers et al ('422) is inapposite for at least the following reasons. *Weers et al.* '422 teaches particles for formulation in metered dose inhalers (MDIs) wherein the particles are suspended in a suspension medium and on use, are propelled into the airway with a propellant. *Weers et al.* is thus directed to the problems of; (i) **stably suspending** the active particles so that they do not aggregate or agglomerate, and (ii) **ensuring chemical and physical compatibility** with non-chlorofluorcarbon propellants (e.g. HFA's and PFC's). *Weers et al* '422 teaches particles engineered to be **suspended** in the suspension medium/propellant, and is not concerned about the behavior of particles in the airway, thus does not teach or suggest the particle or particulate characteristics as claimed by applicants.

Block is nothing more that an academic article, with a disclosure limited, as stated in its title, to investigations into **the solubility and dissolution of triamcinolone acetate**. The mere fact that *Block* discloses a corticosteroid having a solubility less than 1.0 mg/ml adds nothing to *Weers et al.*, as applicants do not hereby assert patentability resides within a specified solubility range.

Patentability of the pending claims resides instead with the claimed elements and features as a whole. *Block* has nothing to do with the preparation of an aerodynamically appropriate particle size for pulmonary administration, and in particular does not relate to an active dispersed in a phospholipid matrix. As such, there is no reason one skilled in the art would seek to combine these (or any other cited) references.

3. Rejection of Under 35 USC 102 (b) over *Kim et al.*

Claims 1-5, 7, 8, 12-15, 17, 18, 20-22, 38-44, 46-49, 51, 53, 69-75, 77-79, 81 and 83 were rejected under 35 USC 102 (b) as anticipated by *Kim et al.*

The Examiner's reliance on *Kim et al*, either individually or in combination with any other cited reference, is misplaced as *Kim et al* does not teach or suggest a particle engineered for inhalation, as defined by **at least** one or more of a particle geometric diameter, a particle size distribution and/or bulk density. In contrast to *Kim et al*, it can be seen from applicants' disclosure that the small particle size range, such as less that about 1 micron as taught by *Kim et al* are unsuitable for inhalation. One reason for such insuitability is that particles of the smaller size range are not retained within the lungs, but are expelled, thus do not have adequate therapeutic activity. *Kim et al* has nothing to do with the preparation of an aerodynamically appropriate particle size for pulmonary administration, and in particular does not relate to an active dispersed in a phospholipid matrix.

Moreover, *Kim et al* does not teach, disclose or suggest applicants' particle size distribution wherein at least 90% of the particles have a geometric diameter of less than 3 microns. As previously pointed out, a discrete and narrow particle size range, as specifically claimed by applicants, is important for pulmonary administration as a powder. This feature is thus one element which distinguishes over references such as Kim *et al*, which do not teach compositions designed or intended for pulmonary administration as a powder. One cannot presume that *Kim et al* teaches **anything at all** about a distribution of particle sizes, and a *prima facie* case of obviousness cannot be established thereby. A particle size **range** is not at all a teaching of a particle size **distribution.** The range of *Kim*

et al is all that is important for making the liquid dispersion, whereas the distribution is important for the inhalable powder of applicants.

Applicants' claims are thus patentably distinct in at least this respect.

4. Rejection of Under 35 USC 102 (b) over *Knight et al*

Claims 1-8, 12-18, 38-44, 46-51, 53, 69-75, and 77-81 were rejected under 35 USC 102 (b) as allegedly anticipated by *Knight et al*, US 5,049,388.

Knight et al is distinct for at least the reasons identified with respect to *Kim et al* and/or *Weers e tal.* above, that is *Knight et al* does not teach or suggest a powder engineered for pulmonary administration, and having at least one or more claimed characteristics of geometric particle size, MMD, or bulk density as claimed by applicant. *Knight et al* is limited to small particle aerosol liposomes: "[t]he field of the invention is small particle aerosol liposomes and liposome-drug combinations advantageous for medical use". Column 1, lines 14-15). Such aerosol liposmes differ from the particulates of applicant in at least the respects of those of *Knight et al* being aqueous particles, comprising a colloid wherein a gas is the continuous phase (see column 1, lines 19-20), and Example 1. Further, *Knight et* al is limited to teaching the formation of liposomes, defined as:

> "Dried phospholipids placed into an aqueous environment will spontaneously associate into multilamellar structures that function as permeability barriers. These lipid vesicles, termed liposomes, are composed of aqueous compartments separated from each other and the external medium by a series of closed concentric lipid bilayers. The composition of the aqueous compartments is the same as the medium in which the liposomes were formed; this makes it possible to entrap a wide variety of materials within the lipid bilayers." Column 1, lines 46-55.

Such liposomes are distinct from the particles of applicants, comprising a phospholipid matrix with active agent dispersed therein, and having the claimed physical characteristics.

Thus as applied to the amended claims, *Knight et al* does not teach, suggest or disclose the specific features or combinations thereof, claimed by applicants.

5. Rejection of Under 35 USC 102(e) over *Weers et al*

Claims 1-22 and 38-83 were rejected under 35 USC 102 (e) as allegedly anticipated by *Weers et al*, US2002/0017295.

Applicant respectfully traverses this rejection based upon Weers et al '295 for the following reasons. While *Weers et al* '295 teaches phospholipid-based powders for inhalation, the '295 application does not teach or disclose a pharmaceutical formulation comprising particulates **consisting essentially** of active agent particles with a **particle size distribution** of at least 90% of the active agent particles having a geometric diameter of less than 3 microns, as recited in amended claims 1, 38 and 54. Instead, the '295 application teaches a larger geometric diameter, and a larger MMAD (see paragraph 0046). Further, there is no teaching of the MMAD, as claimed in claim 2.

Moreover, *Weers* '295 does not teach or suggest the geometric diameter of the active agent particles themselves, nor those of particulates that contain active agent particles. There is no teaching or disclosure in the '295 application that at least 90% the **individual active agent particles** should have a geometric diameter of less than 3 microns or the benefits of the same.

As further applied to amended claim 38, the teachings of the '295 application do not serve the same purpose as the current invention. The present Specification teaches that the claimed insoluble active agent particles are particularly difficult to incorporate into a dispersible medium for pharmaceutical applications. For example, the Background section teaches that "[o]ne particular challenge is to formulate insoluble active agents, such as active agents having a solubility less than 1 mg/ml." This problem of incorporating insoluble active agent into a matrix structure was unexpectedly resolved in the present invention. As taught in the present Specification:

> It has been unexpectedly discovered that it is particularly advantageous for the particle size of the insoluble active agent particles to be below 3.0 μm .... It has been discovered that if the active agent particle size is greater than about 3.0 μm, a heterogeneous composition results comprising active

> agent incorporated in the matrix material and particles comprising active agent without any matrix material. These heterogeneous compositions often exhibit poor powder flow and dispersibility.... [page 13, lines 4-12.]

The unexpected results of a more homogeneous suspension which is obtained by using active agent particles that are insoluble and have sizes below 3 microns, as claimed, are simply not taught or suggested by the '295 application.

6. Rejection of Under 35 USC 103(a) over *Weers et al.* in view of *Cicogna et al.*

Claims 1-22 and 38-83 were rejected under 35 USC 103(a) as allegedly obvious over Weers *et al.*, US2002/0017295, in view of *Cicogna et al.*, Antimicrobial Agents and Therapy, Vol 41 (2) Pages 259-261 (1997)

With regard to one or more of the parameters of MMD, MMAD, particle size distribution, bulk density and crystallinity, it should be noted that the claims have been rejected based on the presumption that it would have been obvious to one skilled in the art to arrive at the claimed composition. Applicants respectfully ask the Examiner to reconsider this overbroad presumption.

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex Inc.*, S. Ct. 1727 (2007); 82 USPQ2d 1385, 1397 (2007), the factors stated in *Graham v. John Deere*, 383, U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry. That is to say, the considerations which must be followed in an inquiry directed to the obviousness or non-obviousness of an invention are as follows:

i. The claimed invention must be considered as a whole;

ii. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and

iii. The references must be viewed without the benefit of hindsight afforded by the claimed invention or accompanying specification.

In conducting the above analysis, one must consider the level of ordinary skill in the art at the time of the invention, as well as whether there exists a reasonable expectation of success.

With regard to the *Weers et al.* reference, the same comments made in regard to the 102 rejections in Paragraph 5 above are similarly applicable here. *Cicogna et al.*

discloses an Amphotericin-B formulation for delivery as an **aerosolized liquid**, not an engineered powder for delivery **as a powder**. *Cicogna et al.* neither discloses nor teaches anything with respect to each of the claimed features of MMD, MMAD, particle size, bulk density, or particle size distribution. Nor, as described with respect to Paragraph 5 above, would on skilled in the art seek to combine *Weers et al.* (or any other cited reference) with *Cicogna et al.*, as the former teaches dry powders, while the latter teaches an aerosolized liquid.

Claim 54 in particular is to a pharmaceutical formulation comprising particulates comprising a crystalline amphotericin B particle in a phospholipid matrix. *Weers et al.* is **devoid of any teaching or suggestion that the bioactive agent particle can be Amphotercin-B, or any antifungal,** and more particularly does not teach or suggest that an Amphotercin-B can be crystalline. Claim 54 further includes the limitations that at least 90% of the crystalline amphotericin B particles have a geometric diameter of less than 3 microns. A crystalline amphotericin B particle in a phospholipid matrix is not taught by *Weers et al.* Further, as explained in the present Specification, amphotericin B is an antimycotic substance. (Specification, page 8, lines 6-12. Emphasis added.) However, neither amphotericin B nor antimycotic substances are taught by *Weers et al.*, which instead, teaches other bioactive agents:

As further explained in the present Specification, it is difficult to incorporate active agents which are crystalline into a pharmaceutical composition because "[s]ignificant interparticle interactions exist for the micron-sized crystals currently used in aerosol delivery, necessitating that the crystals be blended with large lactose carrier particles to improve powder flow and dispersibility." [see Paragraph 0004]. Thus, the cited art does not teach or suggest the advantages of incorporation of a crystalline amphotericin B particle having the claimed size limitations in a phospholipid matrix.

For at least these reasons, claim 54 and the claims that depend therefrom, are patentably distinct over the cited art.

Further, as explained above, the Specification teaches that insoluble active agent particles are particularly difficult to incorporate into a dispersible medium for pharmaceutical delivery. This problem of incorporating such insoluble active agent into a matrix structure was unexpectedly resolved using active agent particles sized less

than 3 microns, as recited in claims 38 and 54. Specifically it was discovered that use of active agents having particle sizes that are below 3 microns result in a more homogeneous pharmaceutical composition in which substantially all the particulates comprise active agent incorporated in the matrix material. The resultant homogeneous composition provides better powder flow and dispersibility and higher drug delivery rates. These unexpected results were obtained by using active agent particles having sizes below 3 microns, and this is not taught or suggested by the *'Weers et al.* Nor, as described above, is there anything to be gained (or any reason for so doing) by combining the teachings of *Cicogna et al.*, with those of *Weers et al.*

For at least these reasons, Independent claims 1, 38, and 54, and their dependent claims are patentable over the cited art.

As the independent claims are allowable over the prior art of record, then their dependent claims are allowable as a matter of law, because these dependent claims contain all features/elements/steps of their respective independent claim. *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Additionally and notwithstanding the foregoing reasons for the allowability of independent claims 1, 38 and 54, the dependent claims recite further features/steps and/or combinations of features/steps (as is apparent by examination of the claims themselves) that are patentably distinct from the prior art of record. Hence, there are other reasons why these dependent claims are allowable.

In view of the above, applicants respectfully request that these grounds of rejection be withdrawn.

Conclusion

In view of the foregoing, applicants submit that pending claims 1-22, 38-42, 44, 47-56, 58, 60, 62-68, and 103 satisfy the requirements of patentability and are therefore in condition for allowance. Reconsideration and withdrawal of all rejections is respectfully requested and a prompt mailing of a Notice of Allowance is earnestly solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to deposit account 50-0348.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 631-3271.

Respectfully submitted,

Date: 10/3/07

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